Keeping 'Em Honest: The Current Crisis of Confidence in Antidepressants

To the Editor: On May 14, 2010, Dr Andrew A. Nierenberg assembled a roundtable conference of experts to address "the current crisis of confidence in antidepressants." In the *Journal* commentary[1] that resulted from this conference, Dr Nierenberg comments, "It is difficult for us to understand the popular perception that industry trials are biased…."[1(p30)]

The problem may not be so much that data from industry trials may not be validly obtained, but, more insidiously, that they may be "spun" by the authors who frequently report small, albeit statistically significant, differences as if they are clinically relevant when they often are not. A good example of this is the notion of the superior efficacy of dual-action or multiaction antidepressants relative to selective serotonin reuptake inhibitors (SSRIs), briefly alluded to by Dr Madhukar Trivedi.[1(p29)]

The notion that certain antidepressants are more efficacious than others was lent credence with the 2001 publication of a meta-analysis of 8 comparative randomized controlled trials (RCTs) by Thase and colleagues[2] that reported a 10% remission rate advantage for venlafaxine over SSRIs. Subsequent meta-analyses using larger data sets found the advantage to be a more modest 6%[3] or 7%.[4] Other meta-analyses of comparative RCTs,[5,6] involving more recently marketed antidepressants, have also touted evidence of superior remission rates relative to conventional SSRIs that were of a magnitude similar to the venlafaxine advantage.[4] This advantage, albeit *statistically* significant, represents only a 1.2-point mean difference[4] on the Hamilton Depression Rating Scale (HDRS),[7] falling well below the 3-point mark of *clinical* significance set by the National Institute for Clinical Excellence (NICE).[8] Thase subsequently coauthored a meta-analysis[9] of trials comparing venlafaxine and other multiaction antidepressants to SSRIs which concluded that 24 patients would need to be treated with a multiaction agent to achieve 1 extra responder (number needed to treat [NNT] = 24). Similarly, their 2008 meta-analysis[10] of studies involving SSRI nonresponders switched either to a second SSRI or to a multiaction agent found a remission rate advantage for the latter group, with an NNT of 22. Although the authors acknowledged in both of these papers that their findings fell well below the mark of an NNT of 10 suggested by the NICE as a minimum threshold of clinical significance, they nonetheless grasped for pertinence, suggesting their findings could be of "public health relevance" given the large numbers of patients treated with antidepressants.[9,10] However, if clinical efficacy differences are negligible at the level of the individual patient, the choice of an antidepressant for that patient should be guided by other factors such as side effect profile and cost.[11]

In 2009, Thase admitted, "Efficacy across all [antidepressant] drug classes is similar but underwhelming."[12] This frank assessment of the evidence concurs with the most recent critical review of antidepressants, whose senior author was Andrew Nierenberg.[11] Yet, Thase and Nierenberg coauthored a 2010 meta-analysis of trials comparing mirtazapine and SSRIs, in which a slight remission rate difference (NNT = 23 in 8-week trials) in favor of mirtazapine-treated patents (who scored, on average, less than a single HDRS point better at endpoint) was presented as "further support for the notion that antidepressants that enhance serotonergic and noradrenergic neurotransmission convey efficacy advantages relative to SSRIs."[13(p196)] Clearly, the interpretation of such minor differences as anything more than clinically negligible is misleading and stands in stark contradiction to their own contemporaneously published assessments on this question.[11,12] Could the other 4 coauthors of this paper[13] (all of whom were employees of the pharmaceutical company that produced mirtazapine at that time) have been more involved in the interpretation ("spinning") of the data than were the distinguished doctors who lent their credibility to this paper?

It is this kind of bias in interpreting the *meaning* of data, rather than bias in the trials that produce these data, that has led to the current crisis of confidence regarding, as well stated by Dr Nierenberg, "whether data can be trusted, whether we can be trusted, and whether our field can be trusted."[1(p30)]

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Eric Teboul, MD
ericteboul@videotron.ca

Author affiliation: Department of Psychiatry, Hôpital Régional de Saint-Jérôme, Saint-Jérôme, Québec, Canada. ***Potential conflicts of interest:*** **Dr Teboul** has received honoraria from AstraZeneca, Eli Lilly, Lundbeck, and Pfizer and has been on the speakers/advisory boards of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Lundbeck, and Pfizer.
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